a. Claim 7, one sentence

Applicants respectfully traverse this rejection. Claim 7 has been amended to contain a period at the end of the claim. Applicants submit that the claim language is now in the form of one sentence and respectfully request that the Examiner reconsider and withdraw this rejection.

b. Claims 4 and 7-10, antecedent basis

Applicants respectfully traverse this rejection. Claim 4 has been amended to indicate that the aqueous pharmaceutical formulation further comprises a tonicity agent. Applicants submit that the claim language of claim 4 no longer requires antecedent basis. Applicants further submit that claim 7 does not contain the language "said tonicity agent" and so the rejection is moot with respect to that claim. Applicants also submit that claims 8-10 now contain sufficient antecedent basis. Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

c. Claim 23, antecedent basis

Applicants respectfully traverse this rejection. Claim 23 has been amended to refer to the pharmaceutical formulation of claim 11. Applicants submit that there is now sufficient antecedent basis for this language. Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

II. Rejection under 35 U.S.C. § 103

Claims 1-23 are rejected under 35 U.S. C. § 103(a) as unpatentable over U.S. 5,045,552 ("Souda *et al.*") in view of Osol *et al.* Applicants respectfully traverse this rejection.

The Office Action states that it is obvious to combine two compositions, each of which is taught by the prior art as useful for the same purpose, in order to form a third composition to be used for the same purpose. Applicants respectfully submit that this is not the case for the instant invention.

The specification states at page 2, lines 4-17:

> It is desirable when preparing reconstituted solutions of such anti-ulcerative compounds that are suitable for intravenous administration, that the solubilized compounds exhibit physical and chemical stability for at least between about 6 and about 12

> hours at room temperature. It has been found by the present inventors that anti-ulcerative compounds such as Compound 1 and the compounds described by general formula I below discolor when they are reconstituted, i.e., dissolved, in aqueous solutions, particularly in solutions suitable for intravenous adminstration, e.g., 5% dextrose or 0.9% saline. Such solutions quickly turn yellow to yellow-brown.
>
> The compounds of the present invention have been determined to be more potent H^+/K^+-ATPase inhibitors than omeprazole sodium. However, in order to provide clinically useful pharmaceutical formulations of the compounds disclosed herein for intravenous administration, it is first necessary to provide formulations for lyophilization and intravenous administration that do not degrade physically, chemically and/or demonstrate a change in color.

The specification further states at page 4, lines 9-19:

> It has now been surprisingly and unexpectedly discovered that if lyophilized compounds of general formula I below are reconstituted in isotonic solutions suitable for intravenous administration, such as 5% dextrose or 0.9% sodium chloride, that have been brought to a pH of between about 9 and about 12, preferably between about pH 10 and 11, by a glycine-sodium hydroxide buffer, such formulations are chemically and physically stable, and do not significantly change color, for at least between about 6 and about 12 hours at room temperature. It was also discovered that the compounds dissolved in such isotonic solutions are stable to color change for from between about 24 and 48 hours if kept at 5 °C. It has also been discovered that the use of glycine buffers with a pH of between about 9 and about 12, preferably between about pH 10 and 11, is beneficial in preparing lyophilized samples of the compounds of the invention.

M.P.E.P. § 716.02(a) states that "Presence of a property not possessed by the prior art is evidence of nonobviousness." (citations omitted). In the instant case, the effect of using a glycine-sodium hydroxide buffer on chemical and physical stablility as well as color was unexpected, as discussed above. Accordingly, Applicants submit that the claimed invention is not obvious over Souda *et al.* in view of Osol *et al.* Applicants therefore request that the Examiner reconsider and withdraw this rejection.

VI. Conclusion.

Applicants respectfully submit that all the bases for rejection of the pending claims are now moot. The Examiner is requested to reconsider the rejections and to withdraw them and to pass this case to issuance.

Respectfully submitted,

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Date: **November 20, 2001**

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Attachments: Marked up copy of amended paragraphs from specification
Copy of pending claims amended with this response
Marked up copy of previous version of claims

Marked-Up Copy of Amended Paragraphs from Specification
U.S.S.N. 09/549,858
Filed April 14, 2000
November 20, 2001

Paragraph at page 16, lines 10-16

It is desirable that the pH of solutions of compound 1 and other compounds of the invention in 5% dextrose or normal saline remain in a range near about pH 10 to provide for an acceptable use period in a clinical setting. Phosphate and glycine buffer systems were tested. Phosphate was found to be an effective buffer in the desired pH range, but, as indicated below, precipitated ~~druing~~**during** freeze-drying of samples containing it; glycine-NaOH was an effective buffer and had a stabilizing effect on color change and may affect turbidity when evaluated with compound 1.

Marked Up Copy of Amended Claims
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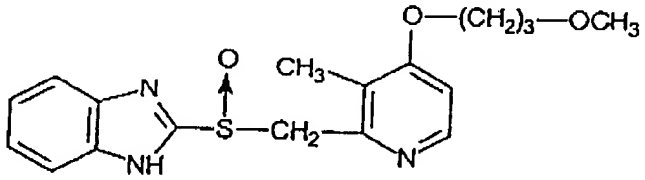
4. (*Amended*) The aqueous pharmaceutical formulation suitable for intravenous injection of claim 1 ~~wherein said~~ **further comprising a** tonicity agent ~~is~~ selected from the group consisting of sodium chloride, glycerin, mannitol, sucrose, lactose, and dextrose.

7. (*Amended*) The aqueous pharmaceutical formulation suitable for intravenous injection of claim 1 wherein said compound is



23. (*Amended*) The **pharmaceutical formulation** ~~method~~ of claim 11, wherein said alkaline pH is between about 9 and about 12.